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(54) Title: METHODS OF HEALING OR PREVENTING INFLAMMATION, DAMAGE AND OTHER CHANGES THAT OCCUR PRIOR TO, DURING OR IMMEDIATELY AFTER A MYOCARDIAL EVENT WITH THYMOSIN BETA 4, ANALOGUES, ISOFORMS AND OTHER DERIVATIVES

(57) Abstract: Inflammation or damage associated with myocardial events is treated or prevented by administration of an angiogenesis-inducing, anti-inflammatory peptide such as Thymosin $\beta 4$, an isoform of Thymosin $\beta 4$ or oxidized Thymosin $\beta 4$.

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METHODS OF HEALING OR PREVENTING INFLAMMATION, DAMAGE AND OTHER
CHANGES THAT OCCUR PRIOR TO, DURING OR IMMEDIATELY AFTER A
MYOCARDIAL EVENT WITH THYMOSIN BETA 4, ANALOGUES, ISOFORMS AND
OTHER DERIVATIVES

BACKGROUND OF THE INVENTION

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of U.S. Provisional Application Serial
No. 60/315,347, filed August 29, 2001.

5 1. FIELD OF THE INVENTION

The present invention relates to the field of healing or preventing inflammation,
damage and other changes that occur in the heart, heart valves and septa just prior to,
during or immediately after a myocardial event (e.g., myocardial infarction).

2. DESCRIPTION OF THE BACKGROUND ART

10 There are many causes of myocardial and coronary vessel and tissue injuries,
including but not limited to myocardial ischemia, clotting, vessel occlusion, infection,
developmental defects or abnormalities and other such myocardial events. Myocardial
infarction results from blood vessel disease in the heart. It occurs when the blood
supply to part of the heart is reduced or stopped (caused by blockage of a coronary
15 artery). The reduced blood supply causes injuries to the heart muscle cells and may
even kill heart muscle cells. The reduction in blood supply to the heart is often caused
by narrowing of the epicardial blood vessels due to plaque. These plaques may rupture
causing hemorrhage, thrombus formation, fibrin and platelet accumulation and
constriction of the blood vessels.

20 There remains a need in the art for improved methods and compositions for
healing or preventing inflammation, damage and other changes that occur prior to,
during or immediately after a myocardial event.

SUMMARY OF THE INVENTION

25 In accordance with the present invention, a method of treatment for promoting
healing or prevention of damage associated with myocardial events involves
administration to a subject or patient in need of such treatment an effective amount of a

composition comprising an angiogenesis-inducing and anti-inflammatory polypeptide comprising amino acid sequence LKKTET or a conservative variant thereof having myocardial event-inhibiting activity.

DETAILED DESCRIPTION OF THE INVENTION

5 The present invention is based on a discovery that actin-sequestering peptides such as thymosin $\beta 4$ (T $\beta 4$) and other actin-sequestering peptides or peptide fragments containing amino acid sequence LKKTET or conservative variants thereof, promote healing or prevention of damage and other changes associated with myocardial events. Included are N- or C-terminal variants such as KLKKTET and LKKTETQ. T $\beta 4$ has been
10 suggested as being a factor in angiogenesis in rodent models. However, there heretofore has been no known indication that such properties may be useful in treating myocardial and coronary vessel events such as myocardial infarction, vessel occlusion or heart valve defects and damage. Without being bound to any particular theory, these peptides may have the capacity to promote repair, healing and prevention by having the
15 ability to induce terminal deoxynucleotidyl transferase (a non-template directed DNA polymerase), to decrease and modulate the levels of one or more inflammatory cytokines or chemokines, and to act as a chemotactic and/or angiogenic factor for endothelial cells and thus heal and prevent degenerative changes in patients afflicted with myocardial events.

20 The present invention provides factors and compositions that can enhance or down regulate mesenchymal epithelial cell differentiation and restore the functionality of damaged myocardium tissue and vessels due to the effects of ischemia, infection, aging, and other insult or injury.

25 Thymosin $\beta 4$ was initially identified as a protein that is up-regulated during endothelial cell migration and differentiation *in vitro*. Thymosin $\beta 4$ was originally isolated from the thymus and is a 43 amino acid, 4.9 kDa ubiquitous polypeptide identified in a variety of tissues. Several roles have been ascribed to this protein including a role in a endothelial cell differentiation and migration, T cell differentiation, actin sequestration and vascularization.

30 In accordance with one embodiment, the invention is a method of treatment for promoting healing and prevention of damage and inflammation associated with myocardial events comprising administering to a subject in need of such treatment an effective amount of a composition comprising an angiogenesis-inducing, anti-

inflammatory peptide comprising amino acid sequence LKKTET, or a conservative variant thereof having angiogenesis-inducing, anti-inflammatory activity, preferably Thymosin β 4, an isoform of Thymosin β 4, oxidized Thymosin β 4, Thymosin β 4 sulfoxide, or an antagonist of Thymosin β 4.

5 Compositions which may be used in accordance with the present invention include Thymosin β 4 (T β 4), T β 4 isoforms, oxidized T β 4, Thymosin β 4 sulfoxide, polypeptides or any other actin sequestering or bundling proteins having actin binding domains, or peptide fragments comprising or consisting essentially of the amino acid sequence LKKTET or conservative variants thereof, having angiogenesis-inducing, anti-
10 inflammatory activity. International Application Serial No. PCT/US99/17282, incorporated herein by reference, discloses isoforms of T β 4 which may be useful in accordance with the present invention as well as amino acid sequence LKKTET and conservative variants thereof having angiogenesis-inducing, anti-inflammatory activity, which may be utilized with the present invention. International Application Serial No.
15 PCT/GB99/00833 (WO 99/49883), incorporated herein by reference, discloses oxidized Thymosin β 4 which may be utilized in accordance with the present invention. Although the present invention is described primarily hereinafter with respect to T β 4 and T β 4 isoforms, it is to be understood that the following description is intended to be equally applicable to amino acid sequence LKKTET, LKKTETQ, peptides and fragments
20 comprising or consisting essentially of LKKTET or LKKTETQ, conservative variants thereof having angiogenesis-inducing, anti-inflammatory activity, as well as oxidized Thymosin β 4.

In one embodiment, the invention provides a method for healing and preventing inflammation and damage in a subject by contacting the damaged site with an effective
25 amount of an angiogenesis-inducing, anti-inflammatory composition which contains T β 4 or a T β 4 isoform. The contacting may be direct or systemically. Examples of contacting the damaged site include contacting the site with a composition comprising T β 4 alone, or in combo with at least one agent that enhances T β 4 penetration, or delays or slows release of T β 4 peptides into the area to be treated. Administration may include, for
30 example, intravenous, intraperitoneal, intramuscular or subcutaneous injections, or inhalation, transdermal or oral administration of a composition containing T β 4 or a T β 4 isoform, etc. A subject may be a mammal, preferably human.

T β 4, or its analogues, isoforms or derivatives, may be administered in any suitable myocardial event damage-inhibiting or -reducing amount. For example, T β 4

may be administered in dosages within the range of about 0.1-50 micrograms of T β 4, more preferably in amounts within the range of about 1-25 micrograms.

A composition in accordance with the present invention can be administered daily, every other day, etc., with a single administration or multiple administrations per day of administration, such as applications 2, 3, 4 or more times per day of administration.

T β 4 isoforms have been identified and have about 70%, or about 75%, or about 80% or more homology to the known amino acid sequence of T β 4. Such isoforms include, for example, T β 4^{ala}, T β 9, T β 10, T β 11, T β 12, T β 13, T β 14 and T β 15. Similar to T β 4, the T β 10 and T β 15 isoforms have been shown to sequester actin. T β 4, T β 10 and T β 15, as well as these other isoforms share an amino acid sequence, LKKTET, that appears to be involved in mediating actin sequestration or binding. Although not wishing to be bound to any particular theory, the activity of T β 4 isoforms may be due, in part, to the ability to regulate the polymerization of actin. β -thymosins appear to depolymerize F-actin by sequestering free G-actin. T β 4's ability to modulate actin polymerization may therefore be due to all, or in part, its ability to bind to or sequester actin via the LKKTET sequence. Thus, as with T β 4, other proteins which bind or sequester actin, or modulate actin polymerization, including T β 4 isoforms having the amino acid sequence LKKTET, are likely to be effective, alone or in a combination with T β 4, as set forth herein.

Thus, it is specifically contemplated that known T β 4 isoforms, such as T β 4^{ala}, T β 9, T β 10, T β 11, T β 12, T β 13, T β 14 and T β 15, as well as T β 4 isoforms not yet identified, will be useful in the methods of the invention. As such T β 4 isoforms are useful in the methods of the invention, including the methods practiced in a subject. The invention therefore further provides pharmaceutical compositions comprising T β 4, as well as T β 4 isoforms T β 4^{ala}, T β 9, T β 10, T β 11, T β 12, T β 13, T β 14 and T β 15, and a pharmaceutically acceptable carrier.

In addition, other proteins having actin sequestering or binding capability, or that can mobilize actin or modulate actin polymerization, as demonstrated in an appropriate sequestering, binding, mobilization or polymerization assay, or identified by the presence of an amino acid sequence that mediates actin binding, such as LKKTET, for example, can similarly be employed in the methods of the invention. Such proteins include gelsolin, vitamin D binding protein (DBP), profilin, cofilin, adsevertin, propomyosin, fincilin, depactin, DnaseI, vilin, fragmin, severin, capping protein, β -actinin and acumentin, for example. As such methods include those practiced in a subject, the

invention further provides pharmaceutical compositions comprising gelsolin, vitamin D binding protein (DBP), profilin, cofilin, depactin, DnaseI, villin, fragmin, severin, capping protein, β -actinin and acumentin as set forth herein. Thus, the invention includes the use of an angiogenesis-inducing, anti-inflammatory polypeptide comprising the amino acid sequence LKKTET (which may be within its primary amino acid sequence) and conservative variants thereof.

As used herein, the term "conservative variant" or grammatical variations thereof denotes the replacement of an amino acid residue by another, biologically similar residue. Examples of conservative variations include the replacement of a hydrophobic residue such as isoleucine, valine, leucine or methionine for another, the replacement of a polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, and the like.

T β 4 has been localized to a number of tissue and cell types and thus, agents which stimulate the production of T β 4 can be added to or comprise a composition to effect T β 4 production from a tissue and/or a cell. Such agents include members of the family of growth factors, such as insulin-like growth factor (IGF-1), platelet derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor beta (TGF- β), basic fibroblast growth factor (bFGF), thymosin α 1 (T α 1) and vascular endothelial growth factor (VEGF). More preferably, the agent is transforming growth factor beta (TGF- β) or other members of the TGF- β superfamily. T β 4 compositions of the invention may reduce the affects of myocardial events by effectuating growth of the connective tissue through extracellular matrix deposition, cellular migration and vascularization of the skin.

In accordance with one embodiment, subjects are treated with an agent that stimulates production in the subject of an angiogenesis-inducing, anti-inflammatory peptide as defined above.

Additionally, agents that assist or stimulate healing of damage caused by a myocardial event may be added to a composition along with T β 4 or a T β 4 isoform. Such agents include angiogenic agents, growth factors, agents that direct differentiation of cells. For example, and not by way of limitation, T β 4 or a T β 4 isoform alone or in combination can be added in combination with any one or more of the following agents: VEGF, KGF, FGF, PDGF, TGF β , IGF-1, IGF-2, IL-1, prothymosin α and thymosin α 1 in an effective amount.

The invention also includes a pharmaceutical composition comprising a therapeutically effective amount of T β 4 or a T β 4 isoform in a pharmaceutically acceptable carrier. Such carriers include those listed above with reference to parenteral administration.

5 The actual dosage, formulation or composition that heals or prevents inflammation, damage and degeneration associated with myocardial events may depend on many factors, including the size and health of a subject. However, persons of ordinary skill in the art can use teachings describing the methods and techniques for determining clinical dosages as disclosed in PCT/US99/17282, *supra*, and the
10 references cited therein, to determine the appropriate dosage to use.

Suitable formulations include T β 4 or a T β 4 isoform at a concentration within the range of about 0.001 - 10% by weight, more preferably within the range of about 0.01 - 0.1% by weight, most preferably about 0.05% by weight.

15 The therapeutic approaches described herein involve various routes of administration or delivery of reagents or compositions comprising the T β 4 or other compounds of the invention, including any conventional administration techniques to a subject. The methods and compositions using or containing T β 4 or other compounds of the invention may be formulated into pharmaceutical compositions by admixture with pharmaceutically acceptable non-toxic excipients or carriers.

20 The invention includes use of antibodies which interact with T β 4 peptide or functional fragments thereof. Antibodies which consists essentially of pooled monoclonal antibodies with different epitopic specificities, as well as distinct monoclonal antibody preparations are provided. Monoclonal antibodies are made from antigen containing fragments of the protein by methods well known to those skilled in the art as
25 disclosed in PCT/US99/17282, *supra*. The term antibody as used in this invention is meant to include monoclonal and polyclonal antibodies.

In yet another embodiment, the invention provides a method of treating a subject by administering an effective amount of an agent which modulates T β 4 gene expression. The term "modulate" refers to inhibition or suppression of T β 4 expression
30 when T β 4 is over expressed, and induction of expression when T β 4 is under expressed. The term "effective amount" means that amount of T β 4 agent which is effective in modulating T β 4 gene expression resulting in effective treatment. An agent which modulates T β 4 or T β 4 isoform gene expression may be a polynucleotide for example. The polynucleotide may be an antisense, a triplex agent, or a ribozyme. For example,

an antisense directed to the structural gene region or to the promoter region of T β 4 may be utilized.

5 In another embodiment, the invention provides a method for utilizing compounds that modulate T β 4 activity. Compounds that affect T β 4 activity (e.g., antagonists and agonists) include peptides, peptidomimetics, polypeptides, chemical compounds, minerals such as zincs, and biological agents.

10 While not be bound to any particular theory, the present invention may promote healing or prevention of inflammation or damage associated with myocardial events by inducing terminal deoxynucleotidyl transferase (a non-template directed DNA polymerase), to decrease the levels of one or more inflammatory cytokines, or chemokines, and to act as a chemotactic factor for endothelial cells, and thereby promoting healing or preventing degenerative changes in cardiac vessels and tissue brought about by myocardial event or other degenerative or environmental factors.

15 The invention is further illustrated by the following example, which is not to be construed as limiting.

Example

Synthetic T β 4 and an antibody to T β 4 was provided by RegeneRx Biopharmaceuticals, Inc. (3 Bethesda Metro Center, Suite 700,, Bethesda, MD 20814) and were tested in a collagen gel assay to determine their effects on the Transformation of cardiac endothelial cells to mesenchymal cells. It is well established that development of heart valves and other cardiac tissue are formed by epithelial-mesenchymal transformation and that defects in this process can cause serious cardiovascular malformation and injury during development and throughout life. At physiological concentrations T β 4 markedly enhances the transformation of endocardial cells to mesenchymal cells in the collagen gel assay. Furthermore, an antibody to T β 4 inhibited and blocked this transformation. Transformation of atrioventricular endocardium into invasive mesenchyme is critical in the formation and maintenance of normal cardiac tissue and in the formation of heart valves.

CLAIMS

1. A method of treatment for promoting healing or preventing damage to coronary tissue, comprising administering to a subject in need of such treatment an effective amount of a polypeptide comprising amino acid sequence LKKTET, or a conservative variant thereof
2. The method of claim 1 wherein said damage results from an injurious myocardial event.
3. The method of claim 1 wherein said polypeptide comprises amino acid sequence KLKKTET or LKKTETQ, Thymosin β 4 (T β 4), an N-terminal variant of T β 4, a C-terminal variant of T β 4, an isoform of T β 4, oxidized T β 4 or T β 4 sulfoxide.
4. The method of claim 1 wherein said composition is administered systemically.
5. The method of claim 1 wherein said composition is administered directly to said coronary tissue.
6. The method of claim 1 wherein said polypeptide is recombinant or synthetic.
7. The method of claim 1 wherein said polypeptide is an antibody.
8. The method of claim 7 wherein said antibody is polyclonal or monoclonal.
9. A method of treatment for promoting healing or preventing damage to coronary tissue, comprising administering to a subject in need of such treatment an effective amount of a composition comprising an agent that stimulates production of an angiogenesis-inducing, anti-inflammatory polypeptide comprising amino acid sequence LKKTET, or a conservative variant thereof having angiogenesis-inducing, anti-inflammatory activity.
10. The method of claim 9 wherein said polypeptide is Thymosin β 4.

11. The method of claim 9 wherein said agent is an antagonist of Thymosin β 4.
12. A composition for use in promoting healing or preventing damage to coronary tissue, comprising an effective amount of a composition including an angiogenesis-inducing, anti-inflammatory polypeptide comprising amino acid sequence LKKTET or a conservative variant thereof having angiogenesis-inducing, anti-inflammatory activity.
13. The composition of claim 12 wherein said composition comprises an N- or C-terminal variant of LKKTET.
14. The composition of claim 12 wherein said composition comprises KLKKTET or LKKTETQ.
15. The composition of claim 12 wherein said polypeptide comprises T β 4, an isoform of T β 4, oxidized T β 4 or T β 4 sulfoxide.

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(54) Title: METHODS OF TREATING MYOCARDIAL EVENT RELATED CONDITIONS WITH THYMOSIN BETA 4

(57) Abstract: Inflammation or damage associated with myocardial events is treated or prevented by administration of an angiogenesis-inducing, anti-inflammatory peptide such as Thymosin β 4, an isoform of Thymosin β 4 or oxidized Thymosin β 4.

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A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : A61K 38/00 US CL : 514/17 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/17, 16, 2; 530/328, 329 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HUFF et al. Beta-Thymosins, Small Acidic Peptides with Multiple Functions. The International Journal of Biochemistry and Cell Biology. 2001, Vol. 33, pages 205-220, see whole document.	1-15
A	HUFF et al. The Dipyrrolyls paraquat and diquat attenuate the interaction of G-actin with thymosin Beta-4. FEBS Letters. 1998, Vol. 425, pages 495-498, see entire document.	1-15
A	WO 96/11016 A1 (ALPHA 1 BIOMEDICALS, INC.) 18 April 1996 (18.04.1996), see entire document.	1-15
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
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